

New Claims 57 and 58 have been added and are directed to a particular subcombination of cytokines recited in Claim 1. No new matter has been added.

The Examiner has withdrawn from consideration new Claims 17-56, submitted by the Applicants on July 9, 2001, as being directed to a non-elected invention. Applicants respectfully reserve the right to later request a rejoinder of withdrawn process claims which depend from or otherwise include all the limitations of any product claim that has been elected, and is subsequently found allowable, in accordance with MPEP § 821.04.

Submitted concurrently herewith is an unexecuted Declaration of Klaus Unsicker under 37 C.F.R. § 1.131. The Applicants note that an executed Declaration will be submitted to the Examiner upon its receipt.

Claim Rejections under 35 U.S.C. §112, second paragraph

The Examiner has rejected Claim 1 as indefinite for the recitation of “a biologically active amount of”. The claim when read in the light of the Specification is clear and simply means that the cytokines have biological activity. However, the Applicants have deleted the phrase for the purpose of clarification. The phrase “functionally active derivatives or parts thereof” was also requested by the Examiner to be clarified. The claim as now amended clearly recites that the functionally active derivatives or parts thereof are in relation to the cited cytokines as defined in the Specification, for example at page 3, line 3-5. Claim 1, as amended, is believed to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

Claim 2 has also been rejected by the Examiner as being indefinite. The amendment to Claim 2 provides further clarification for this claim and is now believed to be definite. Claim 1, on which Claim 2 depends, recites that at least one cytokine is selected from BMP, GDF, TGF- $\beta$  or GDNF. Claim 2, as amended, recites that the second cytokine of the composition is selected from GDF, GDNF, TGF, activin A, BMP, BDNF, NGF, NT, EGF, CNTF or FGF, and that both first and second cytokines are different.

As Claims 1 and 2 are both believed to be definite, dependent Claims 5 and 16 are no longer indefinite for being dependent on an indefinite claim. Withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 U.S.C. §102(b)

Claims 1, 2 and 16 are rejected as being anticipated by Krieglstein *et al.* (Neurochem. Res. 21: 843-850, 1996). The Examiner has stated that "Krieglstein *et al.* teach a composition having neurotrophic activity, comprising TGF- $\beta$  and other cytokines". However, the only compositions that Krieglstein *et al.* teach which have neurotrophic activity are TGF- $\beta$  with NT-3 and TGF- $\beta$  with NT-4. For example, see Abstract, p. 844 last paragraph of Introduction, Figures 4A and 4B, and p.848, first full paragraph. In view of amended Claim 1, Krieglstein does not anticipate the claimed invention.

The Examiner has also stated that the compositions taught by Krieglstein *et al.*, which were used in the culture medium. DMEM, fulfill the limitations of Claim 16 which recites the composition of Claim 1 further comprising a pharmaceutically-acceptable diluent. In fact, Krieglstein *et al.* teach their compositions to be in DMEM supplemented with N1 (a complex mixture of hormones), bovine serum albumin and the antibiotic penicillin. This is not considered a pharmaceutical diluent. It is a cell culture medium for the propagation of cells *in vitro*. One of ordinary skill in the art would only recognize this as cell culture medium, and not as a pharmaceutically-acceptable diluent. Withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 U.S.C. §102(a)

Claim 5 is rejected as being anticipated by Louis (WO 97/19694), published June, 1997.

The Examiner has stated that Louis *et al.* teach a composition having neurotrophic activity, comprising GDNF and TGF- $\beta$ . The Applicants disagree. Louis *et al.* describe the treatment of photoreceptors. Photoreceptors, as described by Louis *et al.*, for example, at page 4, lines 9-10, are a "specialized subset of retinal neurons." These are not representative of neurons in general. They are specialized cells. Furthermore, Louis *et al.* do not teach the use of a cytokine combination for any other cell type, particularly other neuronal cells.

In the interests of expediting the prosecution of this application, Applicants are also submitting concurrently herewith a Declaration Under 37 C.F.R. § 1.131 (the "Declaration"), which submits evidence of the Applicants's conception and reduction to practice of the invention before the Louis *et al.* reference.

This Declaration, by Klaus Unsicker, one of the named inventors of the subject application states and provides evidence that the claimed invention was conceived and reduced to practice with diligence before the publication date of the Louis reference (June, 1997). Specifically, the Declaration includes copies of laboratory notebook pages in which the claimed invention is described and experiments are recorded which detail the reduction to practice of the claimed invention. The present application is a continuation application of PCT/EP98/06004, filed September 21, 1998, which designated the U.S., which claims priority to European patent Application Number 97 116 373.8, filed September 19, 1997, and therefore has the effective filing date of September 19, 1997. In light of the Declaration, the Louis reference is not available as prior art. Withdrawal of the rejection is respectfully requested.

Information Disclosure Statement

A Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Doreen M. Hogle

Doreen M. Hogle

Registration No. 36,361

Telephone: (978) 341-0036

Facsimile: (978) 341-0136

Concord, MA 01742-9133

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MARKED UP VERSION OF AMENDMENTSClaim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Twice Amended) A composition having neurotrophic activity, comprising [a biologically active amount of] at least two cytokines, or functionally active derivatives or parts thereof of said cytokines, wherein at least one of said cytokines is BMP, GDF, TGF- $\beta$  or GDNF, and wherein if a first cytokine is TGF- $\beta$ , then a second cytokine is not NT-3 or NT-4.
2. (Twice Amended) The composition having neurotrophic activity according to Claim 1, wherein the second cytokine[s are] is different from the first cytokine and is selected from the group consisting of GDF, GDNF, TGF, activin A, BMP, BDNF, NGF, NT, EGF, CNTF and FGF.